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Comparing plasma, serum and whole blood indium concentrations from workers at an indium-tin oxide (ITO) production facility

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Abstract

Objective—Occupational exposure to indium compounds including indium-tin oxide (ITO) can result in potentially fatal indium lung disease. We compared plasma, serum and whole blood indium concentrations (In_P, In_S and In_B) from workers at a single ITO production facility to assess the comparability of these matrices used for biological monitoring of indium exposure.

Method—In_P, In_S and In_B were measured using inductively coupled mass spectrometry from consenting workers at an ITO production facility with specimen collection occurring during June–July 2014. Matched pairs from workers were assessed to determine the matrix relationships using the Pearson correlation, paired t-tests, per cent difference, linear regression and κ statistics.

Results—Indium matrices were collected from 80 workers. Mean (SD) In_P, In_S and In_B were 3.48 (3.84), 3.90 (4.15) and 4.66 (5.32) mcg/L, respectively. The In_S–In_P difference was 14%; In_S was higher in all but two workers. In_P and In_S were highly correlated (r=>0.99). The In_B–In_S difference was 19%; In_B was higher in 85% of workers. The In_B–In_P difference was 34%; In_B was higher in 66% of workers. In_B was highly correlated with both In_P and In_S (r=0.97 and 0.96, respectively). κ Statistics were 0.84, 0.83 and 0.82 for In_P, In_S and In_B, respectively, for individuals with each matrix ≥1 mcg/L ($p<0.01$).

Conclusions—While all matrices were highly correlated, we encourage the use of In_P and In_S to reliably compare studies across different populations using different matrices. The higher per cent difference and increased variability of In_B may limit its utility in comparisons with In_P and In_S in different populations.

Occupational exposure to indium compounds including indium-tin oxide (ITO) can result in potentially fatal indium lung disease. The spectrum of disease includes pulmonary alveolar proteinosis that may progress to fibrosis with or without emphysema.[1] Biological monitoring of indium using plasma, serum or blood has served as the foundation to assess

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exposure and prevent adverse health effects in workers exposed to ITO and other indium compounds. However, as there are no reference values for indium in these matrices, the extent to which the selected matrix affects the measurements is unknown.

Exposure to indium is rare and likely occupational in nature when it occurs. However, knowledge of the absorption, distribution and elimination of indium in the human body is limited. The fate of inhaled indium in the body is likely influenced by the chemical form and duration of exposure.[2] Ionic indium that is absorbed into the blood may bind to blood proteins. In one study, the estimated biological half-life of indium in serum was 8.1 years for workers who had quit handling indium for >3 years, but the half-life varied and was longer for those with a higher initial indium burden.[3] Another study has shown that former workers had similar levels of indium in the serum as current workers an average of nearly 5 years since exposure to indium, suggesting indium in the blood represents cumulative exposure with an extended half-life.[4]

To date, epidemiological studies have measured indium concentrations in plasma (In_P) or serum (In_S) to evaluate worker exposure to indium. Results of these studies have been used to establish recommendations and for regulation. In the USA, adverse health outcomes were associated with ≥1 mcg/L In_P.[5] In Japan, a biological exposure limit of 3 mcg/L In_S has been established.[6] Other countries, including Germany and Korea, are also considering developing standards. Whole blood indium (In_B) has been used in the clinical setting to monitor indium exposure. Yet the equivalence of these different matrices has not been evaluated. To assess comparability of these matrices, we analysed In_P, In_S and In_B from workers at a single ITO production facility measured during a narrow timeframe.

METHODS

As part of a longitudinal research study approved by the Institutional Review Board of the National Institute for Occupational Safety and Health (NIOSH), In_P and In_S were collected from consenting workers at an ITO production facility during June–July 2014. Separately, In_B was measured during June–July 2014 as part of the company's medical surveillance programme, and results were provided to NIOSH with study participants' permission.

All measurements were performed by one commercial laboratory using inductively coupled plasma mass spectrometry. For In_P and In_S, the indium analytical method had a limit of detection (LOD) of 0.03 mcg/L and a limit of quantification (LOQ) of 0.1 mcg/L. In_P and In_S values between the LOD and LOQ were reported by the laboratory. For In_B, the LOD was not available and the LOQ was 0.5 mcg/L. Values below the LOQ were not reported by the laboratory.

We compared matched pairs from workers for each matrix. For comparison to In_B, we selected only those who had In_B levels greater than its LOQ. We analysed the subset of workers with each matrix collected in order to assess all three substrates together. We measured matrix agreement for identifying individuals with In_P, In_S and In_B ≥1 mcg/L. We stratified the mean differences of In_B–In_P and In_B–In_S by ≥6 days and <6 days between specimen collection times. Matrix relationships were evaluated using the Pearson

correlation, paired t-tests, per cent difference, linear regression and κ statistics using JMP software V.10.0.1 (SAS Institute, Cary, North Carolina, USA). p Values reported are two sided. We considered p≤0.05 to be significant.

RESULTS

Indium matrices were collected from 80 workers at the ITO production facility during June–July 2014. Of these workers, 86% were men. Sixty-six per cent were white, 8% were black and 10% were Asian; 16% were Hispanic. Median age was 45 years (range: 19–66 years). Median tenure at the ITO facility was 3.4 years (range: 0.1–38 years). Our analyses included 76 workers (95%) with In_P and In_S measured, 53 (66%) with In_P and In_B measured and 50 (63%) with In_S and In_B measured. After removing those without each matrix measured (n=12) and those with In_B below an LOQ of 0.5 mcg/L (n=18), 50 workers were included in the analyses comparing In_P, In_S and In_B. For those individuals with each matrix measured, whole blood was collected at a median of 5.6 days before simultaneous plasma and serum collection, with whole blood collection ranging from 20 days before to 34 days after plasma and serum collection.

Mean (SD) In_P, In_S and In_B were 3.48 (3.84), 3.90 (4.15) and 4.66 (5.32) mcg/L, respectively, for the 50 workers with each exposure matrix collected. The In_S–In_P difference was 14% on average, with individual matched pairs ranging from −0.02 to 2 mcg/L difference; In_S was higher than In_P in all but two workers. In_P and In_S were highly correlated (r=>0.99) (figure 1A). In_B was more variable when compared with both In_P and In_S. The In_B–In_S difference was 19% on average (range: −0.70 to 10 mcg/L difference); In_B was higher in 85% of workers. The In_B–In_P difference was 34% on average (range: −0.21 to 11 mcg/L difference); In_B was higher in 66% of workers. In_B was highly correlated with both In_P and In_S (r=0.97 and 0.96, respectively) (figure 1B, C). κ Statistics were 0.84, 0.83 and 0.82 for In_P and In_S, In_P and In_B and In_S and In_B, respectively, for individuals with each matrix ≥1 mcg/L (p<0.01). The In_B–In_P and In_B–In_S mean differences were not significantly different in workers with specimen collection occurring ≥6 days and <6 days apart (0.84 and 1.47 mcg/L (p=0.22); 0.33 and 1.10 mcg/L (p=0.11), respectively).

DISCUSSION

Our study comparing indium in plasma, serum and blood of workers from a single facility during a narrow timeframe is the first to the best of our knowledge characterising relationships among these three matrices. While In_P, In_S and In_B were highly correlated, we found meaningful differences that should be considered before comparing indium exposures estimated using different matrices.

On average, In_P and In_S had the smallest relative difference of 14%. Seventy-four per cent (97%) of the 76 workers had higher In_S than In_P, suggesting In_P and In_S could be reliably used when comparing indium exposures. Owing to the higher per cent difference and variability, In_B may not be as useful for comparisons to either In_P or In_S in different workforces using the different matrices. In_B was 34% higher than In_P on average; however, in more than one-third (34%) of workers In_B was lower than In_P, In_B shared a similar

relationship with In_S, with In_B being 19% higher on average, but lower in 15% of workers. This is consistent with a 2003 study by Miyaki *et al*[7] comparing biological monitoring of indium using blood, serum and urine in which mean In_B was higher than In_S. Agreement statistics between each matrix were high. Individuals with $In_P \geq 1$ mcg/L, a value associated with adverse health outcomes,[5] generally had In_S and $In_B \geq 1$ mcg/L, suggesting each matrix could be used to detect overexposure to indium.

There are several plausible explanations for indium measuring slightly higher in serum than plasma. In_P was measured using trace metal-free specimen collection tubes. It is possible that the higher mean In_S we observed was due to positive interference during analysis by elements contained in serum collection tubes. Specimen collection and storage can interfere with trace metal measurement.[8] An effect of sample concentration may also account for the higher indium measured in serum than plasma. Fibrinogen is the principal component present in plasma but removed from serum during coagulation.[9] As it lacks fibrinogen, serum is more concentrated than plasma, making it possible that In_S has a higher mean due to the smaller volume fraction in serum than in plasma.

The higher mean and increased variability of In_B compared with both In_P and In_S are likely multifactorial. In addition to the potential issue of elements contained in the collection tubes described above, these differences could involve interaction between indium compounds and the cellular compartment of blood consisting predominantly of red blood cells. However, the higher mean In_B is consistent with a recent study in which 9 (82%) of the 11 metals and trace elements were more concentrated in the whole blood than in the serum.[10] Other factors that could contribute to variability include varying sampling times, and that different instruments with different sensitivities were used. We believe these factors would not substantially affect our results. Most samples were collected during the same week and indium levels in these matrices are indicative of long-term exposure and unlikely to fluctuate during our study window.[11] When we compared the In_B–In_P and In_B–In_S mean differences in workers with sample collection occurring ≥6 days and <6 days apart, we found no significant differences, providing further evidence that sample collection time had limited influence on the results. Moreover, by excluding In_B values below the LOQ in our analyses, the different sensitivities of the instruments unlikely contributed much to variability. Nonetheless, the possibility remains that some of the observed differences reflect when and how blood samples were collected and analysed. Ultimately, further investigation into the absorption, distribution and elimination of inhaled indium compounds may provide a clearer explanation for these differences.

The small sample size precluded the development of correction factors that could be used to adjust concentrations and allow accurate comparisons across populations. However, a factor to account for the consistently higher fraction of indium identified in the serum compared with plasma may be possible with additional data from different workplaces. Likewise, a larger sample size from different workplaces is needed to develop a reliable correction factor for whole blood compared with both plasma and serum, particularly given the variability of indium measured in whole blood compared with the other matrices in our study. While environmental health studies increasingly are quantifying certain metals using various

matrices in different populations,[1012] it is unlikely that reference values will be established for indium as it is not an essential trace element.

In_P, In_S and In_B have been used clinically and/or for epidemiological studies to assess exposure to indium. We measured these matrices that are currently used for biological monitoring in a single workplace during a narrow timeframe. While all three matrices were highly correlated, our study suggests In_P and In_S can be used to reliably compare studies across different populations. While In_B may have value in clinical settings to serially monitor indium exposure of an individual, the higher per cent difference and increased variability measured in this ITO production facility workforce imply limited utility in comparisons with In_P and In_S in different populations using these different matrices.

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What this paper adds

- Indium in plasma, serum and whole blood has been used for biological monitoring of indium exposure in epidemiological studies and/or clinical settings. As there are no reference values for indium in these matrices, the extent to which the selected matrix affects the measurements is unknown.
- While In_P, In_S and In_B were highly correlated, we conclude In_P and In_S are suitable to reliably compare studies across different populations. Owing to the higher per cent difference and increased variability of In_B relative to In_P and In_S in this population, we would urge caution in comparing In_B to In_P or In_S.
- As countries have either already established or are considering standards to limit exposure to indium in occupational settings, our paper helps determine the relationship of different blood matrices used for biological monitoring of indium exposure.

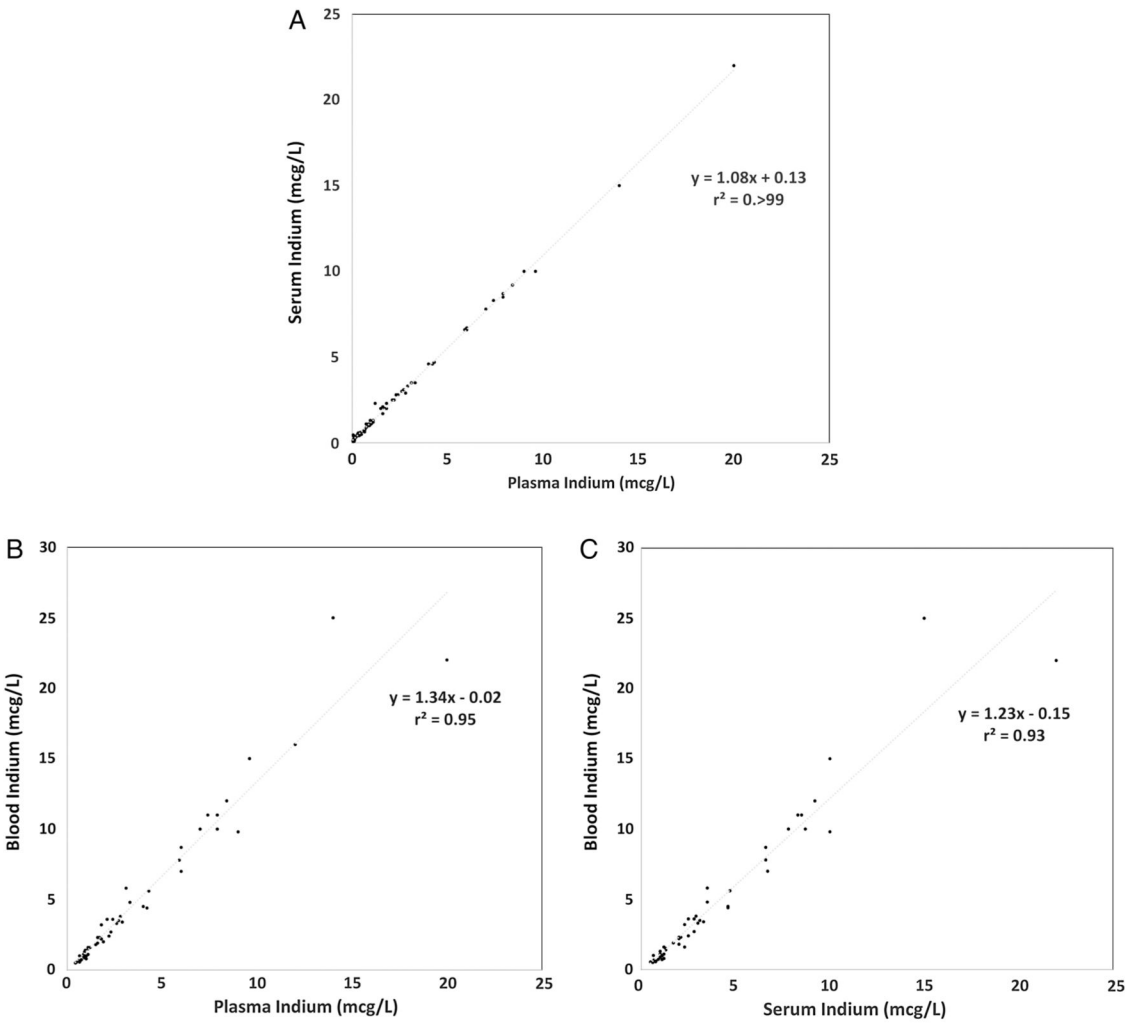

Figure 1.

Blood matrices scatterplots with linear regression lines: (A) In_P and In_S (N=76), (B) In_P and In_B (N=53) and (C) In_S and In_B (N=50). In_B, blood indium; In_P, plasma indium; In_S, serum indium.